Toxic Epidermal Necrolysis Associated with Phenytoin and Cranial Irradiation in Small-Cell Lung Cancer

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Abstract

Background: Toxic epidermal necrolysis (TEN, Lyell disease) is characterized by a widespread bullae formation with epidermal necrosis. TEN occurs mainly in adults, is often attributable to drug sensitivity, and results in full-thickness damage to the epidermis. It is associated with considerable morbidity and mortality.

Case report

A 54-year-old man was diagnosed as having small-cell lung cancer. Phenytoin was administered 300 mg once a day for seizure prophylaxis, after completion of cranial radiotherapy due to solitary brain metastasis. Twelve days after commencing this drug he developed high fever, facial bullae, generalised cutaneous erythematous macules, and targetoid lesions. A skin punch biopsy was performed, and the pathological diagnosis was TEN. The patient was considered to be suffering phenytoin-induced TEN, occurring in up to 80% skin involvement. Complete recovery was achieved after treatment with systemic corticosteroids and antibiotics for septicemia with minimal permanent sequela.

Conclusion: As the first suspicious sign is seen, phenytoin should be discontinued immediately and aggressive medical management should be started.

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Key words: *Toxic epidermal necrolysis, phenytoin, radiation therapy, small-cell lung cancer*

Introduction

Toxic epidermal necrolysis (TEN, Lyell disease) is a severe, idiosyncratic, exfoliative disease of the skin and mucous membranes (1) and is considered to be a severe form of Stevens-Johnson syndrome (SJS) or erythema multiforme. If the damage of the epidermis and lesion of mucous membranes cover up to 30% of the total body surface area it is called TEN, and its annual incidence is about one in a milion (2).

TEN is a potentially life-threatening illness, which has been linked to drug exposure in up to 90% of the cases (1,3). The principal culprits are considered to be sulphonamides, especially the long-acting type, anticonvulsants, antibiotics, allopurinol, and non-steroidal anti-inflammatory drugs (3). Anticonvulsant, phenytoin, may cause this disease (4-6). Radiation therapy may be an inciting (yet uncommon) factor in the occurrence of TEN (7).

The aim of this paper is to report a case of TEN associated with phenytoin and cranial irradiation in small-cell lung cancer.

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Case Report

A 54-year-old man, who had been a tailor living in Eskişehir, Turkey, was diagnosed as having unresectable small-cell lung car-

cinoma by the bronchial biopsy in March 1998. A chemotherapy schedule consisting of carboplatin, etoposide and ifosfamide was begun. After the sixth course of chemotherapy, a cerebral solitary metastasis was detected. Consequently, a cerebral radiotherapy schedule was performed. In addition, a regimen of phenytoin (300 mg/daily) was begun for seizure prophylaxis after cerebral radiotherapy.

Fifteen days after the completion of his cerebral radiotherapy schedule, he was admitted to our clinic as an emergency case. His immediate hospital course was remarkable for high fever, facial bullae, and generalized erythematous macules, erithematous lesions with present Nicolsky sign, eroded areas and targetoid lesions. The cutaneous eruption started on the head and neck and spread in a caudal direction over 3 days to involve nearly his entire body (Figure 1A) (over 80% of total body surface area). There were nasal and buccal erosions and oedema on his face (Figure 1B).

Fever (max 39.3°C), tachypne, hypocapnie and tachycardia were recorded. The breath sound of the lower zone of his right chest was reduced and sonour roncus was heard in his chest. Finger clubbing and 2 cm enlarged liver were present.

Initial laboratory tests showed a normal count of white blood cell and platelet and a normal level of hemoglobin in serum, but the sedimentation rate was high, 82 mm/h. Serum liver enzymes were abnormal with a slightly elevated alanine transaminase and gama glutamyl transpeptidase. Serum lactic dehidrogenase was also high. The serum total protein was 5.1 g/l (normal=6.0-8.5 g/l), and albumine was 2.4 g/l (normal=3.5-5.0 g/l) on admission. Other laboratory tests were normal.

Chest x-ray showed increased density in the right middle zone related to his primary tumour. There was no progression on the size of the lesion, according to his recent chest x-rays.

The patient was presumed to be a severe septisemia, with bad mental status and agitation. Vancomycine plus ciprofloxacine therapy was started with strong support. A topical silver sulphadiazine and betamethasone eye drops were applied every 6 hours and tetracycline ophtalmic ointment was applied every 12 hours. The mouth was frequently toileted with 10% bicarbonate solution and sistemic analgesic was administered.

On the first day of admission all necessary cultures and specimens were obtained for microbiological examination and a punch biopsy was performed on the skin lesion. While there was no microorganism growth in the cultures, the histopathological features led to a diagnosis of toxic epidermal necrolysis (TEN) (Figure 2).

The condition was diagnosed as TEN due to phenytoin,

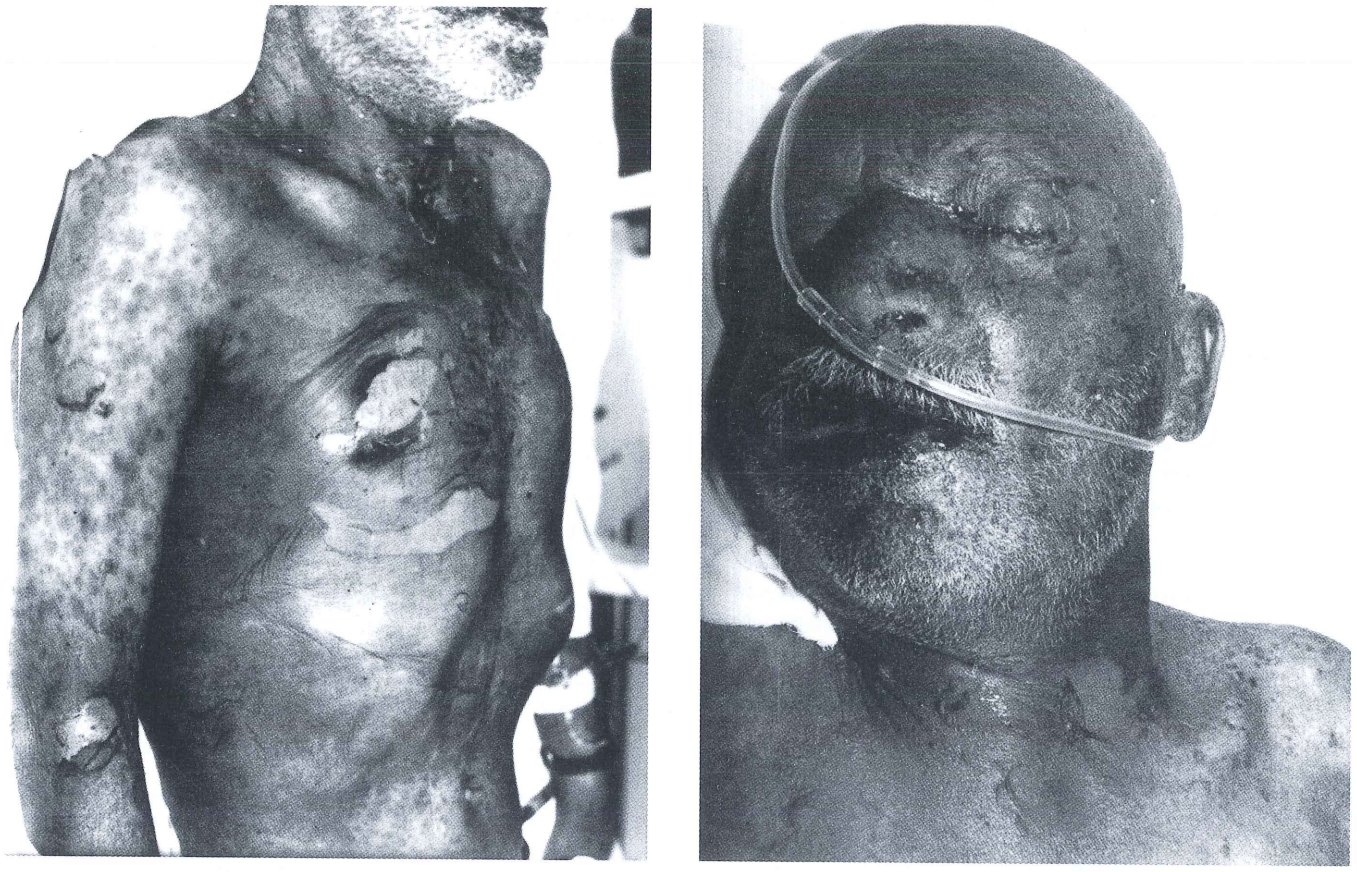

***Fig. 1**. Day 6 of hospitalization. Generalised erythematous macules, erithematous lesions with present Nicolsky sign, eroded areas and targetoid lesions are shown (**1A**). Day 2 of hospitalization. Eye involvement and haemorrhagic buccal mucositis (**1B**).*

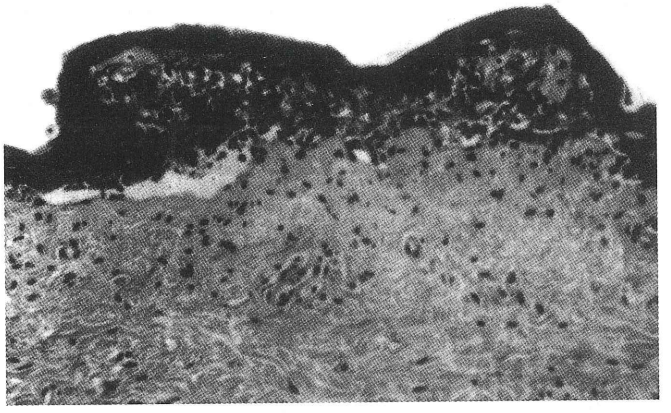

Fig. 2. Histopathologic appearance of the biopsy material (H&E x 80). Epidermis was mildly hyperkeratotic with areas of parakeratosis, hipergranulosis and focal spongiosis. Necrotic keratinocytes were found at all epidermal levels in the fully evolved lesion, and had become confluent to form a thoroughly necrotic blister roof. The bulla was in a subepidermal location. The upper dermis contained a mild lymphocytic inflammatory infiltrate in a largely perivascular arrangement.

involvement of mucous membranes (at least two), and confluence of cutanous lesions causing large areas of necrolysis uncovering the dermis. Since there was an indication of systemic sepsis, ciprofloxacine and vancomycin treatment was administered over 21 days.

The phenytoin treatment was discontinued, and steroid treatment, 60 mg/day, was initiated. On the third day of steroid therapy, the erythematous lesions began to diminish and new bullaes did not develop. For this reason, increase in the dosage was considered unnecessary in the steroid therapy. After the eight-days therapy, daily steroid dosage was decreased by 20 mg every second day, and was discontinued on the fourteenth day. The patient was discharged after a one-month hospital course, with minimal cutaneous sequelae.

Discussion

Toxic epidermal necrolisis (TEN), which is a rarely-reported hypersensitive reaction, was described 42 years ago by Lyell (8). TEN-related mortality rate is 25-30%, and this rate is higher in aged patients at more advanced stages of the disease. The causes of mortality include fluid and electrolyte imbalance and sepsis (9).

Our patient developed extensive TEN as a consequence of phenytoin therapy. A skin biopsy specimen was taken to exclude other dermatoses. Other dermatoses characterized by extensive desquamation include staphylococcal scalded skin syndrome and toxic shock syndrome (10,11).

Radiation therapy may be an inciting factor in the occurrence of TEN (7). Maiche and Teerenhovi report four and Delattre et al. report eight patients suffering erythema multiforme or SJS while receiving cranial irradiation and taking phenytoin (12,13). It is important for physicians to be aware of the synergistic effect between phenytoin and cranial radiation because these therapies are often used together. Phenytoin treatment had also been started in our patient after cranial radiotherapy.

Hypersensitivity to the offending drug is considered to underlie the pathogenesis of TEN. Epidermal necrosis is most probably mediated by a lymphocytotoxic reaction (4).

In a study conducted in Tayland (14), of the 16 patients with a diagnosis of TEN, only one case was found to be related to phenytoin treatment (6.3%). In that study, incubation period for occurrence of phenytoin-induced TEN was found to be 12±8.5 days. In our patient, the time interval between the initiation of phenytoin and the cutaneous eruption is found to be 12 days.

The most important complication of TEN is sepsis (3). Recognition of systemic sepsis in patients with TEN can be difficult. More important signs of serious sepsis in patients with TEN are a drop in core temperature, oliguria, increased respiration rate and an alteration in the patients consciousness (5).

High-dose steroid therapy is suggested to overcome hypersensitivity (1). As the first suspicious sign is seen, phenytoin should be discontinued immediately. Progressive disease still may occur. Aggressive medical management is necessary to ensure the best chance of complete recovery with minimal permanent sequelae.

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